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Association of Accelerometry-Measured Physical Activity and Cardiovascular Events in Mobility-Limited Older Adults: The LIFE (Lifestyle Interventions and Independence for Elders) Study

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Background—Data are sparse regarding the value of physical activity (PA) surveillance among older adults—particularly among those with mobility limitations. The objective of this study was to examine longitudinal associations between objectively measured daily PA and the incidence of cardiovascular events among older adults in the LIFE (Lifestyle Interventions and Independence for Elders) study.

Methods and Results—Cardiovascular events were adjudicated based on medical records review, and cardiovascular risk factors were controlled for in the analysis. Home-based activity data were collected by hip-worn accelerometers at baseline and at 6, 12, and 24 months postrandomization to either a physical activity or health education intervention. LIFE study participants ($n=1590$; age 78.9 ± 5.2 [SD] years; 67.2% women) at baseline had an 11% lower incidence of experiencing a subsequent cardiovascular event per 500 steps taken per day based on activity data (hazard ratio, 0.89; 95% confidence interval, 0.84–0.96; $P=0.001$). At baseline, every 30 minutes spent performing activities ≥ 500 counts per minute (hazard ratio, 0.75; confidence interval, 0.65–0.89 [$P=0.001$]) were also associated with a lower incidence of cardiovascular events. Throughout follow-up (6, 12, and 24 months), both the number of steps per day (per 500 steps; hazard ratio, 0.90, confidence interval, 0.85–0.96 [$P=0.001$]) and duration of activity ≥ 500 counts per minute (per 30 minutes; hazard ratio, 0.76; confidence interval, 0.63–0.90 [$P=0.002$]) were significantly associated with lower cardiovascular event rates.

Conclusions—Objective measurements of physical activity via accelerometry were associated with cardiovascular events among older adults with limited mobility (summary score >10 on the Short Physical Performance Battery) both using baseline and longitudinal data.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01072500. (*J Am Heart Assoc.* 2017;6:e007215. DOI: 10.1161/JAHA.117.007215.)

Key Words: accelerometry • aging • cardiovascular • physical activity

Cardiovascular disease (CVD) is the leading cause of death in the United States and worldwide.¹ In the United States, more than 2200 Americans die every day from cardiovascular-related causes, and persons older than 65 years account for nearly 80% of these deaths.² Older adults also account for nearly 75% of cardiovascular-related

healthcare expenditures.³ Notably, these personal and public health costs are likely to dramatically increase in coming years as the number of Americans 65 years and older is expected to double by the year 2050.⁴

Physical activity (PA) is known to improve health and decrease the risk of developing CVD in a variety of

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Clinical Perspective

What Is New?

- The use of initial and recurring accelerometry measurements may provide useful metrics regarding the impact of older adults' daily lifestyle on cardiovascular risk.
- The present findings suggest that even a single baseline assessment can provide useful information regarding cardiovascular event incidence that can aid in targeting modifiable risk factors.
- This study is one of the first to use accelerometry to explore activity levels and health status among older adults with mobility limitations.

What Are the Clinical Implications?

- Accelerometry measures could serve as an objective, noninvasive, risk monitoring tool for the older adult population.
- Identification of volume and/or intensity of daily physical activity could clinically translate into initial physical activity recommendations and long-term physical activity monitoring and modification.
- Individuals should talk to their healthcare provider before initiating an individual exercise program and discuss what activity levels are recommended for their current health status.
- These findings contribute to an overall wellness recommendation for increased low-level physical activity.

populations.^{5,6} However, less is known regarding the influence of habitual or daily PA in preventing cardiovascular events among older adults. In particular, data are lacking regarding the influence of daily PA on cardiovascular risk among older adults with mobility limitations that restrict the ability to engage in PA.

Although associations between the quantity of PA and cardiovascular risk factors have been reported in older adults, few have made these connections using objective measurements of PA. To date, most studies have relied on self-reported measures of PA, which commonly misclassify the volume and/or intensity of PA.⁶ Although PA has been shown to have an inverse relationship with cardiovascular risk factors and morbidity,⁴ it is unknown whether participation in activity reduces cardiovascular incidence in populations of older adults displaying habitually low levels of PA. Prospective studies to date have largely focused on increasing exercise participation, although formal exercise interventions have been insufficient in reducing the incidence of cardiac events in this population.⁷ However, few studies have utilized objective measurements using accelerometry to evaluate cardiovascular risk in older adults. The benefits of using accelerometry as an objective means to measure

activity levels in older adults have been previously explored.^{8,9} Most notably, these include triaxial measurement of movement in 3 orthogonal directions, so as to capture both linear and rotational movements, and measurement of both duration and intensity of activity. These noninvasive and objective measurement devices do not require participants to undergo training, can be worn without interfering with an individual's daily activities, and precisely measure low levels of activity.

We previously evaluated the association of baseline activity patterns (via triaxial accelerometry) of participants in the LIFE (Lifestyle Interventions and Independence for Elders) study with predicted cardiovascular risk using a Framingham risk prediction model for hard coronary heart disease.¹⁰ This study found that every 25 to 30 min/d spent being sedentary—defined by <100 accelerometry counts per minute—was associated with a 1% higher predicted risk of myocardial infarction (MI) or coronary-related death. Conversely, daily time spent in activities registering 100 to 499 counts per minute was associated with lower predicted hard coronary heart disease risk. Every 30 to 35 minutes of inactivity in this range was also associated with a 1-mg/dL lower circulating high-density lipoprotein cholesterol concentration. Somewhat surprisingly, however, the mean intensity of daily activities was not associated with predicted cardiovascular risk in this population. These data also indicated a significant interaction between sex and activity count for those without CVD, as counts per minute were related to hard coronary heart disease risk in women but not men.

To our knowledge, our prior study was the first to report associations of habitual PA with cardiovascular risk in a clinically representative population of older adults with mobility limitations. However, the cross-sectional nature of the study prevented the ability to draw causal inferences and provided only a projection of cardiovascular risk. Therefore, the overarching objective of the present study is to expand on these prior findings using longitudinal assessment of accelerometry-based PA patterns and the observation of cardiovascular events among this population. This study evaluates the extent to which objective measures of daily PA assessed via accelerometry at baseline and measured longitudinally (0, 6, 12, and 24 months) are associated with cardiovascular events among mobility-limited older adults who participated in the LIFE study.

Methods

Study Overview

The data sets generated and analyzed during the current study are available in the LIFE study repository at <https://www.thelifestudy.org/public/index.cfm>, and are available

from the LIFE study investigators upon reasonable request. The LIFE study was a phase 3 multicenter randomized controlled trial designed to evaluate the efficacy of a long-term PA intervention compared with a successful aging health education (HE) intervention for reducing the incidence of major mobility disability among mobility-limited older adults. Briefly, the LIFE study team randomized 1635 participants from 8 locations throughout the United States and implemented the trial between February 2010 and December 2013. Details about specific study design and implementation of the LIFE study have been previously reported.^{11,12} Institutional review boards at all participating sites approved the study protocol, and written informed consent was obtained from all study participants. The trial was monitored by a data and safety monitoring board appointed by the National Institute on Aging and was registered at <http://www.clinicaltrials.gov> (NCT01072500) before participant recruitment.

Participants and Study Entry

Details about specific recruitment strategies and inclusion criteria for the LIFE study have been previously reported.^{11,12} Briefly, participants were eligible for the study if they: (1) were between the ages of 70 and 89 years, (2) were at high risk for mobility disability based on objectively measured lower-extremity functional limitations, (3) were able to walk 400 m in ≤ 15 minutes, (4) reported spending < 20 min/wk performing moderate to vigorous PA, (5) displayed satisfactory cognitive function, and (6) were able to safely participate in the PA and HE interventions. A thorough medical screening was performed to ensure the safety of potential participants. The screening included an initial telephone screening, a prescreening visit where the study was presented to the participant, a question and answer session, a prescreening consent form, tests of physical performance, and the Community Healthy Activities Model Program for Seniors (CHAMPS) PA questionnaire¹³ to confirm sedentary lifestyle. This questionnaire assesses engagement in moderate-intensity activities as well as engagement in all specified physical activities to discern the frequency and duration of PA usually undertaken by an older adult.

Study Interventions

Participants were randomized to either the PA or HE intervention via a secure, web-based data management system using a permuted block algorithm (with random block lengths) stratified by field center and sex. Both intervention groups received an initial individual 45-minute face-to-face question and answer session, in which a health educator explained the intervention, communicated expectations, and answered questions.¹⁴

The PA intervention involved walking (with a goal of 150 min/week), strength, flexibility, and balance training.¹¹ The intervention included attendance at 2 center-based visits per week and home-based activity 3 or 4 times per week for the duration of the study. A protocol was in place to restart the intervention for the participants who suspended PA for medical reasons. The PA intervention sessions were individualized and progressed toward a goal of 30 minutes of walking daily at moderate intensity, 10 minutes of primarily lower extremity strength training by means of ankle weights (2 sets of 10 repetitions), 10 minutes of balance training, and large muscle group flexibility exercises. The participants began with lighter intensity and gradually increased the intensity over the first 2 to 3 weeks of the intervention. The Borg scale of self-perceived exertion,¹⁵ which ranges from 6 to 20, was used to measure intensity of activity. Participants were asked to walk at an intensity of 13 (activity perception “somewhat hard”), and lower extremity strengthening exercises were performed at an intensity of 15 to 16. Further details regarding the training program are available elsewhere.^{11,13}

Participants in the HE intervention were assigned to attend small group sessions weekly for the first 26 weeks and monthly thereafter. The educational sessions included topics relevant to older adults and were intended to increase awareness relative to a variety of health topics including how to effectively negotiate the healthcare system, medications, foot care, preventive services and screenings recommended at different ages, how to travel safely, and nutrition. Each session concluded with a short instructor-led program (5–10 minutes) of upper extremity stretching exercises. Information relative to PA was purposely avoided, with the exception of a PA brochure presented to participants during the first HE session.

Accelerometry

Daily PA was objectively measured using a hip-worn, solid-state triaxial accelerometer (ActiGraph GT3X) at 0, 6, 12, and 24 months. Participants were asked to wear the device at all times—except while bathing, sleeping at night, or swimming—for a minimum of 7 consecutive days. Movement was captured along the vertical axis in 1-second epochs, and nonwear time was classified using a previously published algorithm¹⁶ that flags areas where there is a 90-minute time window of zero counts per min after allowing a 2-minute interval of nonzero counts for artifactual movement detection. We limited our analyses at each time point (0, 6, 12, and 24 months) to participants who wore the device for at least 10 hours per day for a minimum of 3 days. Participants with valid data for at least one time point were included in the present analyses. Currently, there are no well-accepted,

evidence-based accelerometry cut points for PA in mobility-limited older adults. Therefore, the cut point for PA was chosen based on current best practices from the literature. Sedentary behavior was defined as <100 counts per minute¹⁷ and PA was categorized as activities registering ≥100 counts per minute. Furthermore, PA was divided into 2 incremental intensity categories identified by accelerometer-detected ranges of 100 to 499 counts per minute and activities registering ≥500 counts per minute.

Assessment of Cardiovascular Events

At each 6-month contact, participants (or a proxy informant if the participant was not available) were questioned about all hospitalizations since the last visit. Hospital records were obtained to abstract for the standard criteria for the primary and secondary outcomes, blinded to intervention assignment. The primary outcome in the LIFE study was major mobility disability, while total CVD was a predefined secondary outcome and included MI, silent MI, hospitalized angina, congestive heart failure, revascularization with bypass surgery or percutaneous angioplasty, aortic aneurysm, peripheral artery disease, stroke, and transient ischemic attack. Records and abstraction forms were sent to the coordinating center for central review by 2 physician-investigators, with adjudication as definite, probable, or not confirmed by 2 reviewers. If there were differences between reviewers, cases were adjudicated by consensus of the full committee. Only definite events were included in this report.

Reports of death were tracked through regular surveillance and death certificates were obtained to supplement the hospital record review. Silent MI was assessed by ECGs obtained at 18 and 36 months and read at a central reading center. The time from randomization date to the first cardiovascular event, fatal or nonfatal, was used to define incidence during the trial. Analyses were conducted and assessed for the overall sample and stratified according to history versus no history of CVD.

Statistical Analysis

Baseline characteristics including randomization, demographic characteristics, and self-reported disease history were summarized using means (SDs) for continuous measures and counts (percentages) for discrete measures. A series of Cox proportional hazards regression models stratified by field center and sex were used to explore the association between accelerometry measures and cardiovascular events. Event time was defined as the time from randomization to the initial CVD event and censoring time as the time from randomization to the last assessment or death.

Five baseline daily accelerometry measures of interest were included in this analysis one at a time: total activity counts, total step counts, sedentary time (minutes of activity count <100 counts per minute), minutes of activity count ≥500 counts per minute, and 30-minute peak cadence. Model 1 adjusted for randomization and accelerometer wear time. Model 2 added race, age, education, marital status, and whether a participant lived alone. Model 3 further added history of diabetes mellitus, history of CVD, use of antihypertensive drugs, and use of lipid-lowering drugs. Finally, Model 4 further added systolic blood pressure, diastolic blood pressure, ankle-brachial index, and Pittsburgh Sleep Quality Index (PSQI) scores. The analyses were performed using R (survival package).¹⁸ Considering multiple comparisons, a conservative Bonferroni correction with $P<0.01$ ($P=0.05/5$ for 5 individual accelerometry measures).

To study how different levels of PA were associated with cardiovascular events, 2 intensity levels: (1) minutes of activity counts 100 to 499 counts per minute, and (2) minutes of activity counts ≥500 counts per minute, were included in a model simultaneously. Because the model was adjusted for accelerometer wear time, the third PA intensity level, (3) sedentary time, was not fitted to avoid singularity. The interaction between the 2 intensity levels was also tested. The interaction was removed from the model when not significant. Each accelerometry measure was also defined as a time-dependent variable and refitted to allow for time-dependent covariates. Time-varying covariate models used accelerometry data at baseline to assess association with CVD events in the interval from 0 to 6 months; 6-month PA data for associations with CVD events during 6 to 12 months; 12-month PA data for associations with CVD events during 12 to 24 months; and 24-month PA data for associations with CVD events at >24 months. Additional analyses included: (1) testing the interaction between each PA measure and randomization, (2) a sensitivity analysis to evaluate the influence of CVD history on outcomes, and (3) the evaluation of the association between self-reported moderate-intensity PA as measured by the CHAMPS questionnaire and cardiovascular events.

Results

Data from a total of 1590 LIFE participants were included in the present study. Forty-five participants did not have sufficient valid accelerometry data, and were therefore excluded from the present analysis. The mean (\pm SD) age of included participants was 78.9 ± 5.2 years, 67.2% were women, and 23.6% were racial/ethnic minorities. Just over a third of participants were married (35.9%), and the majority of participants reported having a college education (63.8%). In general, participants were cognitively intact as evidenced by scores on the Modified Mini-Mental State Examination (3MS)

Table 1. Demographic Characteristics of Study Participants

	Full Sample (N=1590)	PA Arm (n=790)	HE Arm (n=800)
Women	1069 (67.2)	525 (66.5)	544 (68.0)
Age	78.9±5.2	78.7±5.2	79.1±5.2
Nonwhite	375 (23.6)	200 (25.3)	175 (21.9)
Living alone	780 (49.1)	371 (47.0)	409 (51.1)
Married	571 (35.9)	288 (36.5)	283 (35.4)
Education: college or higher	1015 (63.8)	497 (62.9)	518 (64.8)
CESD score	8.5±7.8	8.3±7.7	8.8±7.9
PSQI score	5.9±3.8	5.9±3.8	5.9±3.8
3MS score	91.7±5.4	91.7±5.5	91.7±5.3
Self-reported history of cardiovascular-related conditions			
Myocardial infarction	125 (7.9)	59 (7.5)	66 (8.3)
Congestive heart failure	69 (4.3)	25 (3.2)	44 (5.5)
Stroke	106 (6.7)	55 (7.0)	51 (6.4)
Lung disease	246 (15.5)	124 (15.7)	122 (15.3)
Diabetes mellitus	397 (25.0)	187 (23.7)	210 (26.3)
Other self-reported CVD	311 (19.6)	150 (19.0)	161 (20.1)
Smoking status			
Current	703 (44.2)	371 (47.0)	332 (41.5)
Former	47 (3.0)	24 (3.0)	23 (2.9)

Data are expressed as mean±SD or number (percentage). 3MS indicates Modified Mini-Mental State Examination; CESD, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; HE, health education; PA, physical activity; PSQI, Pittsburgh Sleep Quality Index.

(91.7±5.4 points), showed low levels of depressive symptoms according to Center for Epidemiologic Studies Depression Scale (CESD) scores (8.5±7.8), and had relatively poor sleep quality according to PSQI scores (5.9±3.8). Based on

self-report, 7.9% of participants experienced a previous MI, 4.3% reported a history of congestive heart failure, and 19.6% reported a history of other cardiovascular conditions. For the present study, a total of 234 cardiovascular events were included (HE:PA=113:121) for a total incidence of 14.7%. Additional detail regarding participant demographic characteristics is provided in Table 1.

At baseline, participants wore accelerometers for a mean of 7.95±3.24 valid wear days and 837.1±111.1 min/d (ie, ≥10 h/d). They spent 647±116 min/d of their baseline wear time (647/837=77%) being sedentary (ie, <100 counts per minute). The remaining (nonsedentary) time was spent in activity registering 100 to 499 counts per minute (137±43 min/d) with a smaller portion (53±38 min/d) spent performing activities registering ≥500 counts per minute. Participants also accrued 2681±1475 steps per day with a peak average cadence of 34.8±17.2 steps per 30 minutes during the baseline measurement period.

The association of baseline accelerometry measures with incidence of cardiovascular events is shown in Table 2 (individual PA). Most notably, every 30 minutes spent engaging in activities registering ≥500 counts per minute was associated with a 25% decrease in cardiovascular event risk ($P=0.001$). At baseline, participants had an 11% lower chance of experiencing a subsequent cardiovascular event per 500 steps taken per day ($P=0.001$). Meanwhile, every 30 min/d spent being sedentary was associated with a 13% increase in risk of cardiovascular events ($P=0.002$) after adjustment. Total number of activity counts per day was also negatively associated with the risk of cardiovascular event ($P=0.001$), while peak cadence of activity was not significantly associated with cardiovascular event risk. There were no significant interactions of any of these accelerometry measures with the randomized arm (all P values >0.05). The

Table 2. Association of Baseline Accelerometry Measures With Cardiovascular Event Risk

	Accelerometry Measure	Model 1	Model 2	Model 3	Model 4
Individual	Total step counts (500 steps)	0.86 (0.80–0.91)*	0.86 (0.80–0.92)*	0.89 (0.83–0.95)*	0.89 (0.84–0.96)*
	Sedentary time (30 min)	1.19 (1.10–1.27)*	1.18 (1.09–1.27)*	1.14 (1.06–1.23)*	1.13 (1.04–1.22)*
	Min/d ≥500 counts/min (30 min)	0.67 (0.57–0.79)*	0.68 (0.58–0.80)*	0.74 (0.63–0.87)*	0.75 (0.65–0.89)*
	Total activity counts (10 000 counts)	0.90 (0.87–0.94)*	0.91 (0.87–0.95)*	0.93 (0.89–0.97)*	0.93 (0.89–0.97)*
	Peak 30-min cadence, steps per min	0.98 (0.97–0.99)*	0.98 (0.97–0.99)*	0.98 (0.97–1.00)*	0.99 (0.97–1.00)*
Joint	Min/d 100 to 499 counts per min (30 min)	0.98 (0.85–1.12)	0.97 (0.85–1.12)	0.97 (0.85–1.12)	0.99 (0.85–1.14)
	Min/d ≥500 counts per min (30 min)	0.68 (0.57–0.83) [†]	0.70 (0.57–0.85) [†]	0.75 (0.62–0.92) [†]	0.76 (0.62–0.93) [†]

Data are expressed as hazard ratios (95% confidence intervals). Sedentary time was defined as minutes per day <100 counts per minute. All models adjusted for accelerometer wear time. Model 1 stratified for site and sex, and adjusted for randomization. Model 2 adjusted for model 1, race, age, education, living alone, and marital status. Model 3 adjusted for model 2, diabetes mellitus, cardiovascular disease, and antihypertensive use. Model 4 adjusted for model 3, ankle-brachial index, systolic and diastolic blood pressure, and Pittsburgh Sleep Quality Index score.

*If $P<0.01$ (Bonferroni corrected for multiple accelerometry measures) for individual physical activity measure model fit.

[†]If $P<0.05$ for joint physical activity measures model fit.

models were fitted with 2 levels of activities at baseline, minutes of activity 100 to 499 counts per minute, and minutes of activity ≥ 500 counts per minute, simultaneously. Minutes of activity ≥ 500 counts per minute was negatively associated with cardiovascular risk after adjusting for minutes of activity 100 to 499 counts per minute and other covariates, while minutes of activity 100 to 499 counts per minute was not associated with cardiovascular event risk, as shown in Table 2 (joint PA). The interaction between minutes of 100 to 499 counts per minute and ≥ 500 counts per minute was not significantly associated.

Across all data collection visits, participants spent 648 ± 114 min/d of their wear time (78.2%) being sedentary (ie, < 100 counts per minute). The remaining time was spent in activity registering 100 to 499 counts per minute (131 ± 44 min/d) and ≥ 500 counts per minute (51 ± 35 min/d). Participants also accrued 2625 ± 1545 steps per day. Accelerometry data across study visits are shown for all participants in Table 3.

The longitudinal association of accelerometry measures with cardiovascular events based on time-varying models is shown in Table 4. Using these longitudinal data, minutes per day spent engaging in activities registering ≥ 500 counts per minute had the strongest association with cardiovascular events ($P=0.002$). In addition, every 500 steps taken were associated with a 10% decrease in cardiovascular event risk ($P=0.001$), as well as a 6% decrease in cardiovascular event risk for every 10 000 activity counts recorded ($P=0.003$). There were no significant interactions of any accelerometry measures with treatment group (all P values > 0.05). Moreover, sensitivity analyses revealed that CVD history did not influence associations of any PA exposures with cardiovascular events (all P values > 0.05). Lastly, self-reported PA via the CHAMPS questionnaire was not significantly associated with events in either the baseline model (hazard ratio, 1.00; 95% confidence interval, 0.97–1.04) or the longitudinal model (hazard ratio, 0.99; confidence interval, 0.96–1.02). Similar to the baseline PA joint model, minutes of activity counts ≥ 500 counts per minute was negatively associated with cardiovascular event risk, while minutes of activity counts 100 to 499 counts per minute was not associated with cardiovascular event risk. However, the interaction between minutes of 100 to 499 counts per minute and ≥ 500 counts per minute was significant for cardiovascular event incidence, as shown in Table 4 (Joint PA).

Discussion

The national burden of morbidity and mortality caused by CVD events remains high,² calling for cost-efficient and effective preventative measures. Regular engagement in PA is an important factor in maintaining cardiovascular health, and as

Table 3. Accelerometry-Measured Physical Activity Data by Randomized Arm and Visit

	Baseline		6 mo		12 mo		24 mo	
	PA (n=666)	HE (n=671)	PA (n=646)	HE (n=656)	PA (n=653)	HE (n=661)	PA (n=681)	HE (n=588)
Sedentary time, min/d	649.4 \pm 120	644.8 \pm 112.4	635.4 \pm 112.8	640.6 \pm 105.3	634.3 \pm 96.1	640.8 \pm 103.4	642.4 \pm 102.8	654.9 \pm 107.3
Time spent 100 to 499 counts per min, min/d	137.2 \pm 42.7	137.4 \pm 43.7	136.2 \pm 42.5	133.7 \pm 43.7	130.7 \pm 43.3	129.9 \pm 43.3	127.9 \pm 44.4	123.3 \pm 43.5
Time spent ≥ 500 counts per min, min/d	52.6 \pm 35.3	52.7 \pm 38.0	56.7 \pm 33.9	49.5 \pm 33.9	53.5 \pm 34.9	47.5 \pm 32.5	48.9 \pm 34.2	43.6 \pm 33.2
Activity counts per d	90 295.1 \pm 47 516.4	90 585 \pm 51 167	99 709.8 \pm 52 479.5	86 642.7 \pm 45 367.2	94 626.5 \pm 53 096.2	83 985.8 \pm 45 067.5	87 021.1 \pm 50 410.3	77 720.5 \pm 44 766.9
Steps per d	2665.4 \pm 1390.1	2698.4 \pm 1555.6	3200.6 \pm 1689.3	2576.9 \pm 1435.8	3003.8 \pm 1678.4	2516.1 \pm 1417.3	2705.4 \pm 1625.7	2281.2 \pm 1450.1
30-min peak cadence, steps per min	34.9 \pm 17	34.7 \pm 17.3	44.2 \pm 21.3	34.2 \pm 17.5	41 \pm 20.3	33.9 \pm 17.3	36.5 \pm 20	31 \pm 17

Data are expressed as mean \pm SD. Sedentary time is defined as minutes per day < 100 counts per minute. HE indicates health education; PA, physical activity.

Table 4. Association of Longitudinal, Time-Varying, Accelerometry Measures With Cardiovascular Event Risk

	Accelerometry Measure	Model 1	Model 2	Model 3	Model 4
Individual	Total step counts (500 steps)	0.87 (0.82–0.92)*	0.87 (0.82–0.92)*	0.89 (0.84–0.95)*	0.90 (0.85–0.96)*
	Sedentary time (30 min)	1.15 (1.07–1.24)*	1.15 (1.07–1.24)*	1.11 (1.03–1.20)*	1.10 (1.02–1.19)*
	Min/d ≥ 500 counts per min (30 min)	0.68 (0.58–0.80)*	0.68 (0.57–0.81)*	0.73 (0.62–0.81)*	0.76 (0.63–0.90)*
	Total activity counts (10 000 counts)	0.92 (0.88–0.95)*	0.92 (0.88–0.95)*	0.93 (0.89–0.97)*	0.94 (0.90–0.98)*
	Peak 30-min cadence, steps per min	0.98 (0.97–0.99)*	0.98 (0.97–0.99)*	0.98 (0.97–0.99) [†]	0.98 (0.97–0.99)*
Joint	Min/d 100 to 499 counts per min (30 min)	0.92 (0.77–1.09)	0.91 (0.77–1.08)	0.92 (0.78–1.10)	0.92 (0.77–1.10)
	Min/d ≥ 500 counts per min (30 min)	0.37 (0.23–0.60) [†]	0.37 (0.23–0.61) [†]	0.42 (0.25–0.71) [†]	0.40 (0.24–0.68) [†]
	Interaction	1.12 (1.03–1.23) [†]	1.13 (1.03–1.23) [†]	1.11 (1.01–1.22) [†]	1.13 (1.03–1.24) [†]

Data are expressed as hazard ratios (95% confidence intervals). Sedentary time is defined as minutes per day <100 counts per minute. All models adjusted for accelerometer wear time. Model 1 stratified for site and sex, and adjusted for randomization. Model 2 adjusted for model 1, race, age, education, living alone, and marital status. Model 3 adjusted for model 2, diabetes mellitus, cardiovascular disease, and antihypertensive use. Model 4 adjusted for model 3, ankle-brachial index, systolic and diastolic blood pressure, and Pittsburgh Sleep Quality Index score.

*If $P < 0.01$ (Bonferroni corrected for multiple accelerometry measures) for individual physical activity measure model fit.

[†]If $P < 0.05$ for joint physical activity measures model fit.

such, several scientific and public health bodies have created minimum PA guidelines for improving cardiovascular health.^{6,19,20} However, despite these guidelines, questions remain about the proper prescription of PA among several populations—including older adults with mobility limitations. In fact, although these guidelines were created to apply to all adults, the gradations of cardiovascular risk among mobility-limited older adults who may be unable to meet these recommendations are unknown. Thus, objective measurements of PA, such as those obtained by accelerometers, which accurately classify the volume and/or intensity of PA, may assist in refining PA recommendations for this population.

The primary finding of this study is that objective measurement of PA via accelerometry was significantly associated with incidence of cardiovascular events among older adults with limited mobility. These findings suggest that the use of initial and recurring accelerometry measurements may provide useful metrics regarding the impact of seniors' daily lifestyle on cardiovascular risk. This noninvasive measure does not require participant training and provides objective data for monitoring and assessing CVD risk. In fact, the present findings suggest that even a single baseline assessment can provide useful information regarding cardiovascular event incidence, which can aid in targeting modifiable risk factors. The aim for future use of accelerometry data includes identification of likelihood of experiencing a cardiovascular event based on habitual activity levels, and not the reduction of cardiovascular risk through the use of an exercise intervention.

Notably, the present study did not indicate a significant interaction between accelerometry measures and the randomized arm in relation to cardiovascular events. This finding is in line with results from recent large, longitudinal

clinical trials—including the LIFE study—indicating limitations in structured activity interventions for reducing CVD incidence among high-risk populations.^{7,21} It remains possible that responses to interventions may not be observed because baseline levels of activity as even small amounts of daily activity may provide CVD protection—although more studies in this area are needed to confirm this hypothesis. In addition, the present study did not indicate an association of self-reported PA from the CHAMPS survey with CVD. As has been previously explored,⁷ this could be attributable to a lack of sensitivity from self-report as well as a potential issue of intensity in the way in which CHAMPS is graded. While accelerometry is capable of accurately capturing low levels of PA, the CHAMPS survey may not be graded in a way that allows for a precise measurement of low-level activity.

Study Strengths and Limitations

The present study had several strengths including a clinically relevant study population, multisite design, relatively large sample size, and use of an objective measurement of PA. Limitations of this analysis include missing accelerometry data, the lack of generalizability of conclusions to populations other than older, mobility-limited adults, and the potential for residual confounding.

Still, these data do suggest that accelerometry measures could serve as an objective, noninvasive, risk monitoring tool for the older adult population. Identification of volume and/or intensity of daily PA could clinically translate into initial PA recommendations, and long-term PA monitoring and modification. Individuals should talk to their healthcare provider before initiating an individual exercise programs and discuss what activity levels are recommended for their current health

status. While individuals in this population should be discussing individual exercise programs with a healthcare provider before initiating an exercise program, these findings contribute to an overall wellness recommendation for increased low-level PA. An increase in habitual activity could be a way to decrease time spent sedentary and allow individuals to benefit from the health advantages of engagement in low-level PA. Clinically, healthcare professionals can discuss the benefits of low-level activity outside of formal exercise. This assessment tool may also allow researchers to target additional modifiable risk factors in combination with adjustments in daily activity levels. Presently, however, the lack of established guidelines for classifying accelerometry measures in this population limits the ability to immediately translate these findings into public health recommendations. This study is one of the first to use accelerometry to explore activity levels and health status among older adults with mobility limitations. While public health guidelines recommended 150 minutes of moderate to vigorous activity per week, many individuals in this population are unable to participate in this level of activity.

Conclusions

Previous studies^{10,22} and the current findings show that lower levels of activity may be potentially warranted, as there are health benefits related to the amount of activity individuals in this population may be capable of engaging. While accelerometers are an expensive research tool that produce data which may be difficult for a member of the general population to interpret, pedometers are a low cost and easy-to-use alternative device for individuals to clinically monitor their daily activity duration and step count. While accelerometry could potentially be used as an additional vital sign to aid in clinical guidance for determining overall health and risk, more research is ultimately needed to interpret accelerometry data on an individual level and for provision of recommendations in a clinical setting.

Appendix

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Disclosures

None.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:434–441.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322.
3. Hodgson TA, Cohen AJ. Medical care expenditures for selected circulatory diseases: opportunities for reducing national health expenditures. *Med Care*. 1999;37:994–1012.

4. Ortman J, Velkoff V, Hogan H. An aging nation: the older population in the United States. 2014;P25-1140.
5. Luke A, Dugas LR, Durazo-Arvizu RA, Cao G, Cooper RS. Assessing physical activity and its relationship to cardiovascular risk factors: NHANES 2003–2006. *BMC Public Health*. 2011;11:387.
6. US Department of Health and Human Services. Physical activity guidelines advisory committee report, 2008. To the secretary of health and human services. *Nutr Rev*. 2009;67:114–120.
7. Newman AB, Dodson JA, Church TS, Buford TW, Fielding RA, Kritchevsky S, Beavers D, Pahor M, Stafford RS, Szady AD, Ambrosius WT, McDermott MM; LIFE Study Group. Cardiovascular events in a physical activity intervention compared with a successful aging intervention: the LIFE Study randomized trial. *JAMA Cardiol*. 2016;1:568–574.
8. Taraldsen K, Chastin SF, Riphagen II, Vereijken B, Helbostad JL. Physical activity monitoring by use of accelerometer-based body-worn sensors in older adults: a systematic literature review of current knowledge and applications. *Maturitas*. 2012;71:13–19.
9. Falck RS, McDonald SM, Beets MW, Brazendale K, Liu-Ambrose T. Measurement of physical activity in older adult interventions: a systematic review. *Br J Sports Med*. 2016;50:464–470.
10. Fitzgerald JD, Johnson L, Hire DG, Ambrosius WT, Anton SD, Dodson JA, Marsh AP, McDermott MM, Nocera JR, Tudor-Locke C, White DK, Yank V, Pahor M, Manini TM, Buford TW; LIFE Study Research Group. Association of objectively measured physical activity with cardiovascular risk in mobility-limited older adults. *J Am Heart Assoc*. 2015;4:e001288. DOI: 10.1161/JAHA.114.001288.
11. Fielding RA, Rejeski WJ, Blair S, Church T, Espeland MA, Gill TM, Guralnik JM, Hsu FC, Katula J, King AC, Kritchevsky SB, McDermott MM, Miller ME, Nayfield S, Newman AB, Williamson JD, Bonds D, Romashkan S, Hadley E, Pahor M; LIFE Research Group. The lifestyle interventions and independence for elders study: design and methods. *J Gerontol A Biol Sci Med Sci*. 2011;66:1226–1237.
12. Marsh AP, Lovato LC, Glynn NW, Kennedy K, Castro C, Domanchuk K, McDavitt E, Rodate R, Marsiske M, McGloin J, Groessl EJ, Pahor M, Guralnik JM; LIFE Study Research Group. Lifestyle interventions and independence for elders study: recruitment and baseline characteristics. *J Gerontol A Biol Sci Med Sci*. 2013;68:1549–1558.
13. Rejeski WJ, Axtell R, Fielding R, Katula J, King AC, Manini TM, Marsh AP, Pahor M, Rego A, Tudor-Locke C, Newman M, Walkup MP, Miller ME; LIFE Study Investigator Group. Promoting physical activity for elders with compromised function: the lifestyle interventions and independence for elders (LIFE) study physical activity intervention. *Clin Interv Aging*. 2013;8:1119–1131.
14. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, King AC, Kritchevsky SB, Manini TM, McDermott MM, Miller ME, Newman AB, Rejeski WJ, Sink KM, Williamson JD; LIFE Study Investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. 2014;311:2387–2396.
15. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377–381.
16. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. *Med Sci Sports Exerc*. 2011;43:357–364.
17. Ekelund U, Luan J, Sherar LB, Esliger DW, Griew P, Cooper A; International Children's Accelerometry Database (ICAD) Collaborators. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *JAMA*. 2012;307:704–712.
18. Therneau T, ed. *A Package for Survival Analysis in S. Version 2.38*. 2015. <https://CRAN.R-project.org/package=survival>.
19. Exercise for health. WHO/FIMS committee on physical activity for health. *Bull World Health Organ*. 1995;73:135–136.
20. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2960–2984.
21. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145–154.
22. Mankowski RT, Anton SD, Axtell R, Chen SH, Fielding RA, Glynn NW, Hsu FC, King AC, Layne AS, Leeuwenburgh C, Manini TM, Marsh AP, Pahor M, Tudor-Locke C, Conroy DE, Buford TW. Device-measured physical activity as a predictor of disability in mobility-limited older adults. *J Am Geriatr Soc*. 2017;65:2251–2256.